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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/189,415	11/10/1998	BRETT B FINLAY	07422/013001	5485

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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/189,415	FINLAY ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,23,28,52 and 60-74* is/are pending in the application.

4a) Of the above claim(s) *6, 23, 60-62, 64, 66, 73 and 74* is/are withdrawn from consideration.

5)☒ Claim(s) *7* is/are allowed.

6)☒ Claim(s) *52,63,65 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Election

1) Acknowledgment is made of Applicants' election of the polypeptide species comprising the amino acid sequence of SEQ ID NO: 11 filed 03/16/05 in response to the species election requirement mailed 01/21/05.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 07/12/04, 11/05/04, 03/16/05 and 08/01/05 in response to the non-final Office Action mailed 02/11/04. With this, Applicants have amended the specification and the raw sequence listing.

Status of Claims

3) Claims 1-5, 8-22, 29-51 and 53-59 have been canceled via the amendments filed 07/12/04 and 11/05/04.

Claims 6, 7, 23 and 52 have been amended via the amendment filed 07/12/04.

New claims 60-74 have been added via the amendment filed 07/12/04.

Claims 73 and 74 have been amended via the amendment filed 11/05/04.

Claims 24-28 have been canceled via the amendment filed 03/16/05.

Claims 72 has been amended via the amendment filed 03/16/05.

Claims 6, 7, 23, 52 and 60-74 are pending.

Claims 6, 23, 60-62, 64, 66, 73 and 74 have been withdrawn from consideration as not being directed to the elected invention or species. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 7, 52, 63, 65 and 67-72 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the drawings made in paragraph 5 of the Office Action mailed 02/11/04 is withdrawn in light of Applicants' submission of formal drawings filed 07/12/04.

7) The objection to the specification made in paragraph 8 of the Office Action mailed 02/11/04 is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Moot

8) The rejection of claims 1-5 and 52-59 made in paragraph 9 of the Office Action mailed 02/11/04 under 35 U.S.C § 112, first paragraph, as containing inadequate written description rejection, is withdrawn in light of Applicants' cancellation of the claims.

10) The rejection of claims 1-5 and 52-59 made in paragraph 10 of the Office Action mailed 02/11/04 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' cancellation of the claims.

11) The rejection of claims 53-59 made in paragraph 11 of the Office Action mailed 02/11/04 are rejected under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' cancellation of the claims.

12) The rejection of claim 3 made in paragraph 13(a) of the Office Action mailed 02/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' cancellation of the claim.

13) The rejection of claims 6 and 7 made in paragraph 13(b) of the Office Action mailed 02/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' cancellation of the claims.

14) The rejection of claim 52 made in paragraph 13(c) of the Office Action mailed 02/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' cancellation of the claim.

15) The rejection of claim 59 made in paragraph 13(d) of the Office Action mailed 02/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' cancellation of the claim.

16) The rejection of claims 4-7 and 53-59 made in paragraph 13(e) of the Office Action mailed 02/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of

Applicants' cancellation of the claims.

17) The rejection of claims 1, 3-5, 52, 53, 55, 57 and 59 made in paragraph 15 of the Office Action mailed 02/11/04 under 35 U.S.C. § 102(b) as being anticipated by Rosenshine *et al.* (*EMBO J.* 15: 2613-2624, 03 June 1996 – Applicants' IDS) (Rosenshine *et al.*, 1996) as evidenced by Kenny *et al.* (*Cell* 91: 511-520, 14 November 1997 – Applicants IDS), is withdrawn in light of Applicants' cancellation of the claims.

18) The rejection of claims 52-54, 56 and 58 made in paragraph 17 of the Office Action mailed 02/11/04 under 35 U.S.C § 103(a) as being unpatentable over Rosenshine *et al.* (1996) (*EMBO J.* 15: 2613-2624, 03 June 1996 – Applicants' IDS), is withdrawn in light of Applicants' cancellation of the claims.

Specification – New Matter

19) The specification is objected to for the following reasons:

(i) The specification is objected to under 35 U.S.C. § 132, because they introduce new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention.

(a) The 'RDEC-1' polypeptide is identified in the amended Figure 9A-B description on page 7, lines 27-28 as 'SEQ ID NO: 14', whereas line 16 of page 49, as amended, refers to 'RDEC-1' 'polypeptide' to be 'SEQ ID NO: 12'. The raw Sequence Listing as originally filed did not contain 'SEQ ID NO: 12'. Both the recitation of 'SEQ ID NO: 12' now added on page 49 and its sequence composition now added to the raw Sequence Listing filed 08/01/05 constitute new matter.

(b) The recitation 'SEQ ID NO: 5 nucleotide' added at line 16 of page 49 of the specification via the amendment filed 07/12/04 is new matter. This part of the specification, as originally filed, did not describe any 'nucleotide' having a specific SEQ ID number of 'RDEC-1'.

(c) The raw Sequence Listing filed 08/01/05 includes the recitation and composition of 'SEQ ID NO: 13', which was absent in the Sequence Listing originally filed. The recitation of 'SEQ ID NO: 12' on page 49 and its sequence composition as disclosed in the raw Sequence Listing filed 08/01/05 both constitute new matter.

(ii) The specification lacks reference to, or antecedent basis for, 'SEQ ID NO: 2', 'SEQ ID NO: 4', 'SEQ ID NO: 6' and 'SEQ ID NO: 13', which sequences are included in the raw Sequence Listings filed 11/10/98 and 08/01/05, but are not referred to in the specification.

(iii) The amendments made to line 16 of page 49 of the specification and the brief description for Figures 9A-B are confusing and/or inconsistent. At line 16 of page 49 of the specification, the 'RDEC-1' polypeptide is identified in the amended description for Figures 9A-B on page 7, lines 27-28 as 'SEQ ID NO: 14', whereas line 16 of page 49, as amended, refers to 'RDEC-1' 'polypeptide' to be 'SEQ ID NO: 12'.

Rejection(s) Based on Applicants' Amendments

Rejection(s) under 35 U.S.C. § 101

20) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

21) Claim 65 and those dependent therefrom are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claim 65, as written, do not sufficiently distinguish over fusion proteins as they exist naturally for example on EPEC or EHEC bacteria, because the claim does not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of --an isolated Tir polypeptide-- as is supported in the instant specification. See MPEP 2105.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

22) Claim 52 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 52, as amended, includes the newly added limitations: polypeptide 'that comprises at least one of the amino acid sequences set forth in SEQ ID NO: 10 and SEQ ID NO: 11'. By

this, a polypeptide comprising both of the amino acid sequences set forth in SEQ ID NO: 10 and SEQ ID NO: 11 is encompassed within the scope of the claim. However, there appears to be no descriptive support in the instant specification as originally filed for the now claimed pharmaceutical composition comprising a single polypeptide that comprises both SEQ ID NO: 10 and SEQ ID NO: 11. Therefore, the limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

23) Claim 69 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 69, as amended, includes the newly added limitations: wherein the Tir polypeptide 'has at least one amino acid residue in SEQ ID NO: 11' substituted with a conservative amino acid and wherein the Tir polypeptide 'has at least one amino acid .... Inserted into SEQ ID NO: 11 .... wherein the Tir polypeptide retains at least one Tir-specific antibody'. The term 'at least' has no upper limit and therefor includes indefinite number. However, there appears to be no descriptive support in the instant specification as originally filed for a polypeptide comprising an amino acid sequence that is substantially identical to SEQ ID NO: 11, wherein any number of amino acids is substituted, deleted or inserted as recited currently. Therefore, the above-identified limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the originally filed specification where support for

such recitations can be found.

24) Claims 70-72 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 70 depends from new claim 69. The isolated Tir polypeptide of claim 69 comprising an amino acid sequence that is substantially identical to SEQ ID NO: 11 wherein the Tir polypeptide (i.e., Tir variant) has at least one amino acid residue in SEQ ID NO: 11 substituted with a conservative amino acid, or at least one amino acid deleted from or inserted into SEQ ID NO: 11, wherein the Tir polypeptide retains at least one Tir-specific activity. Dependent claims 70-72 are drawn to Tir variant polypeptides which retain at least the ability to bind to intimin, the ability to nucleate actin in a host cell, the ability to activate a host cell signal transduction pathway, the ability to specifically bind to a Tir-specific antibody, or the ability to induce an immune response in a host to an organism that produces a Tir polypeptide, such as, enteropathogenic *E. coli* or enterohemorrhagic *E. coli*. However, such Tir polypeptides (i.e., variants) having the specifically recited Tir-specific activity is not supported in the specification, as originally filed. Furthermore, recitations such as 'host cell signal transduction pathway' and nucleate actin 'in a host cell' appear to lack descriptive support in the specification, as originally filed. Therefore, the limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Enablement)

25) Claims 69-72 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to an isolated altered Tir polypeptide, i.e., Tir polypeptide variant, having at least one Tir-specific activity. The recitations 'has at least one amino acid residue in SEQ ID NO: 11 substituted with a conservative amino acid' and 'has at least one amino acid deleted from or inserted into SEQ ID NO: 11' in claim 69 encompass substitution, deletion or insertion of more than one amino acid within SEQ ID NO: 11, and within or outside an epitope of SEQ ID NO: 11. In addition to having the above-identified amino acid substitution, deletion or insertion, the claimed Tir polypeptide variant is *required* to retain 'at least one Tir-specific activity': (a) the ability to bind intimin; (b) the ability to nucleate action in a host cell; (c) the ability to activate a host cell signal transduction pathway; (d) the ability to specifically bind to a Tir-specific antibody; or (e) the ability to induce an immune response in a host to enteropathogenic or enterohemorrhagic *E. coli* that produces a Tir polypeptide. A review of the instant specification indicates that other than the polypeptide of SEQ ID NO: 11, no other Tir polypeptides modified as recited in the instant claims are enabled that *concurrently* have at least one of the recited Tir-specific activity. This is important because obtaining an altered polypeptide as recited, which retains a Tir-specific biologic activity by substitution with one or more conservative amino acids, or by deletion from or insertion into a Tir polypeptide, is not a predictable event. Predictability or unpredictability is one of the *Wands* factors for enablement. A review of the art on bacterial polypeptides indicates that even a single amino acid (let alone more than one) change within a bacterial polypeptide, within an epitope or even outside an epitope, are associated with loss of biologic activity or specificity. There is absolutely no showing of a correlation between the primary or tertiary structure of the claimed Tir polypeptide variant of SEQ ID NO: 11 and its Tir-specific activity. There is no showing that the Tir polypeptide variant tolerates one or more recited

modifications and remain Tir-specific. With this lack of showing, the Office would look into the literature in the relevant art of polypeptide variants in order perform the required *Wands* analysis. A review of the state of the art at the time of the invention, particularly with regard to unpredictability associated with biologic functions of bacterial polypeptide variants, reveals the following. The art shows that an alteration in a single even amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991) showed that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in 'striking changes in the structural and immunological properties of the class 1 protein' of this isolate (see abstract and page 514). With particular reference to VR1 and VR2 epitopes of Class 1 outer membrane protein of *Neisseria meningitidis*, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) also taught that '[a] single amino acid change *within an epitope*, or an amino acid deletion *outside an epitope*, were both associated with *loss of subtype specificity* resulting from a change in the predicted conformation at the apex of the loop structure' (see abstract) [Emphasis added]. One of skill in the art can reasonably expect a loss of one or more Tir-specific activities in Applicants' polypeptide variant having the recited amino acid substitution, deletion, or insertion. The lack of disclosure and specific guidance within the instant specification combined with the art-recognized functional unpredictability as explained above would require one of skill in the art to engage in considerable undue experimentation.

With regard to polypeptides in general, Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences (i.e., fragments), or even in different positions of the same sequence' (see page 3). The lack of guidance within the instant specification in combination with Rudinger's teachings further emphasize the unpredictability factor and the need to engage in considerable undue experimentation.

The state of the art on microbial polypeptides in general indicates that a random replacement affecting the epitopic amino acid positions that are critical to the three-dimensional conformational

structure and specific binding property of a protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool. [Emphasis added]

Thus, it has already been established in the art that variations in critical residues at specific positions of an amino acid sequence could result in a polypeptide variant, which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In other words, although a polypeptide having one or more amino acid substitution, deletion, or insertion in the native Tir polypeptide comprising the amino acid sequence of SEQ ID NO: 11 is likely to be immunogenic, there is no predictability that such a variant would remain Tir-specific and retain at least one Tir-specific activity, including the ability to induce an immune response in a host to a Tir-producing organism, such as, enteropathogenic or enterohemorrhagic *E. coli*. Thus, the above-cited references reasonably demonstrate that even a single amino acid substitution/deletion will often dramatically affect the immunospecific biological activity or characteristics of a protein.

With regard to the conservative amino acid substitution, the art reflects that it is not predictable to retain the same function(s) in a polypeptide or protein by substitution of even one (let alone more than one) amino acid residue with another amino acid residue of similar polarity. For instance, Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) showed that a substitution of Leu with Ala in a protein resulted in a complete loss of functional or biologic activity of the protein. Lazar *et al.* taught that they 'did not expect that a mutation of Leu to Ile (which have similar a size and polarity) would cause such a strong effect' (see paragraph bridging left and right columns on page 1251; and third full paragraph on page 1251, right column). Clearly, with the amino acid substitution, deletion, or insertion in the native Tir polypeptide of SEQ ID NO: 11 as recited in the instant claims, the Tir-specific function(s) of the claimed polypeptide variant cannot be predicted, nor would it be expected to be substantially identical to that of the polypeptide of SEQ ID NO: 11.

Although a skilled artisan might envision making a number of changes in the reference polypeptide sequence of SEQ ID NO: 11 in accordance with Applicants' disclosure, it is highly uncertain that the polypeptide variant as recited would retain at least one of the recited Tir-specific activity. Furthermore, if one nucleotide in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 11 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 11. For these reasons, making and using of the instantly claimed polypeptide variant having at least one of the recited Tir-specific activity is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the microbial polypeptide art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

26) Claims 69-72 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 69 is vague and indefinite in the recitation 'substantially identical to the sequence set forth in SEQ ID NO: 11', because it is unclear what degree of identity to SEQ ID NO: 11 constitutes 'substantial identity'. How much of SEQ ID NO: 11's original structure has to be retained such that the resulting sequence can be considered as 'substantially identical to the sequence set forth in SEQ ID NO: 11', is not clear. The metes and bounds of the structure encompassed in the limitation 'substantially identical to the sequence set forth in SEQ ID NO: 11' is indeterminate.

(b) Claim 69 is further vague and indefinite in the recitation 'Tir-specific activity', because it is unclear what activities are encompassed in this limitation. What qualifies as a 'Tir-specific activity', and whether this is a biologic or non-biologic activity is not clear.

(c) Claims 70-72, which depend from claim 69, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

27) Claim 63 is rejected under 35 U.S.C § 102(b) as being anticipated by Webster *et al.* (*Mechanisms of Development* 38: 25-32, 1992).

Webster *et al.* taught a 524 amino acid-long polypeptide comprising the at least eight amino acid-long fragment, TTTTTTTTTTTTS, which shows 100% sequence identity with amino acids 393-404 of the instantly recited SEQ ID NO: 11. See amino acid residues 105-116 of the amino acid sequence depicted in Figure 4. The 524 amino acid-long prior art polypeptide is large enough to serve inherently as an immunogen.

Claim 63 is anticipated by Webster *et al.*

Remarks

28) Claims 52, 63, 65 and 67-72 stand rejected. Claim 7 is free of prior art currently of record.

29) Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

30) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses or papers is (571) 273-

8300.

31) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

32) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

October, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER